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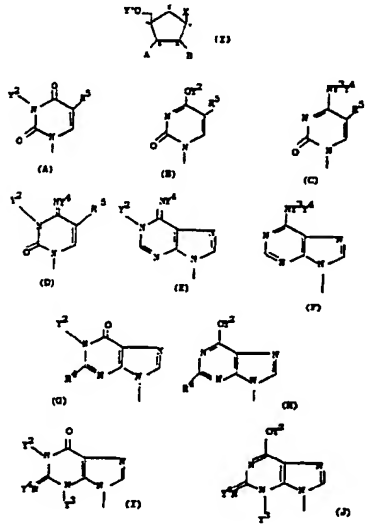
(54) Title: CARBO-NUCLEOSIDE DERIVATIVES

(57) Abstract

A carbo-nucleoside derivative characterised in that it corresponds to general formula (I) wherein ------ represents optional unsaturation; A represents H or sustituent which is F or OH; B represents H or a substituent which is F; Y^1 represents H or a physiologically-acceptable group corresponding to the formula: $R^1(O)_nCO(OCR^2R^3)_m$- wherein n represents 0 or 1; m represents 0 or 1; R^1 represents an optionally unsaturated and/or optionally substituted alkyl, alkyloxyalkyl or aryl group or an N-(C_1-C_7 alkyl)-1,4-dihydropyridin-3-yl group or, when n represents O, H; R^2 and R^3 independently represents H, C_1-C_6 alkyl C_2-C_6 alkenyl or alkynyl or aryl; alternatively, two of such substituents may be replaced by an alkylidene group; and X represents a group selected from (A), (B), (C), (D), (E), (F), (G), (H), (I), (J) wherein Y^2, Y^3 and Y^4 independently have the same definition as Y^1; R^4 represents H or -NY^3Y^4, Y^3 and Y^4 being as defined above; and R^5 represents H or halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl or trifluoromethyl; provided that at least one of Y^1, Y^2, Y^3 and Y^4 represents other than H and that, when all of Y^2, Y^3 and Y^4 present represent H, then Y^1 represents $R^1(O)_nCO(OCR^2R^3)_m$ wherein n and/or m represents 1; and/or salts thereof is disclosed.



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Carbo-nucleoside Derivatives

This invention relates to carbo-nucleoside derivatives; more particularly, it relates to antiviral esters, ethers and amides of carbo-nucleoside derivatives which, inter alia are active against human immunodeficiency virus (HIV), the retrovirus which causes the disease acquired immunodeficiency syndrome (AIDS).

Since the recognition of AIDS as a new clinical entity in 1981, nearly five hundred thousand cases of the disease have probably been diagnosed, while the number of HIV-infected persons is estimated to be between 5 and 10 million. AIDS is fatal, more than 50% of all diagnosed cases having ended in death. HIV and AIDS are today and will remain a worldwide health problem for many years to come.

Clinical symptoms are weight loss, chronic diarrhoea, persisting fever and opportunistic infections due to loss of T-cells, thus upsetting the overall balance of the immune system. The patient loses his/her ability to combat otherwise insignificant infections.

Several different methods to combat the infection have been tried. Among the methods tried are stimulation of the immune system and conventional treatment of the (secondary) life-threatening infections. So far the most promising method has been to attack the replication of the HIV-virus. Several events in the replicative cycle may be considered as targets for chemotherapeutics, however, the most successful target so far has been reverse transcriptase.

Many substances interfering with replication have been tried, e.g. 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyadenosine, 2',3'-dideoxycytidine, 2'-chloro-2',3'-dideoxyadenosine, 2',3'-dideoxyguanosine, 2',3'-dideoxyinosine, 2',3'-dideoxy-2'3-didehydrothymidine, 3'-azido-2',3'-dideoxyuridine, 3'-azido-2',3'-dideoxy-5-ethyl-uridine, 1-(2-deoxy-2-fluoro-ß-D-

arabinofuranosyl)-5-ethyluracil, 2,6-diamino-9-(3-azido-2,3-dideoxy-ß-D-erythropentofuranosyl)purine, suramin, Evans Blue, fuchsin acid, 5-chloro-3'-fluoro-2'3'-dideoxy-uridine, hypericin, 1-aurothioglucose, carbovir, dextran sulphate, interferon alpha, monoclonal antibodies against HIV envelope, peptide T, phosphonoformate (foscarnet), phosphorothioate oligodeoxynucleotides, protease inhibitors, ribavirin and soluble CD4 receptor.

EP-A- 196185, for instance, describes pharmaceutical compositions containing AZT, a known compound which has shown great promise in the treatment of AIDS and AIDS-related complex. It is believed that AZT works by inhibiting reverse transcriptase, a vital enzyme in the life cycle of retroviruses.

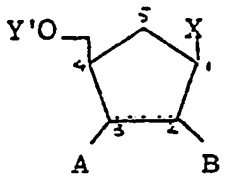
Further work has been done on alternative reverse transcriptase inhibitors which might avoid the limitations and drawbacks of AZT, for instance bone marrow suppression or the need for frequent administration of relatively large quantities, and among those suggested have been fluorinated nucleosides and cyclopentyl analogues.

The synthesis of some of these compounds has been described, see EP 277599 (Asahi); EP 325460 (Minnesota); EP 346132 (Minnesota); AIDS research and human retroviruses, 4, 457, (1988); Biochem. Pharmacol., 37, 2847, (1988); J. Med. Chem., 31, 2040, (1988); J. Med. Chem., 32, 1743, (1988); and J. Med. Chem., 30, 2131, (1987).

It has been found that acylation or alkylation of oxygen atoms in the 5'-position or in the purine or pyrimidine ring and/or acylation or alkylation of exocyclic or endocyclic nitrogen atoms present in the purine or pyrimidine ring may give significant advantages in terms of uptake, overall activity and site of action. WO 88/07532 describes certain esters and amides of this type carrying acyl groups on the oxygen in at the 5' position or in the heterocycle or on exocyclic or endocyclic nitrogens; this

principle has been extended to a wider range of related compounds.

The present invention provides carbo-nucleoside derivatives which correspond to the following general formula (I):



wherein

the dotted bond .... represents preferred, but optional, unsaturation;

A represents H or a substituent which is F or OH;

B represents H or a substituent which is F;

(preferably, for a saturated compound, if B represents F, A represents OH, while for an unsaturated compound, A or B represents F and the other represents H);

Y^1 represents H or a physiologically-acceptable group corresponding to the formula:

$$R^1(O)_nCO(OCR^2R^3)_m-$$

wherein n represents 0 or 1;

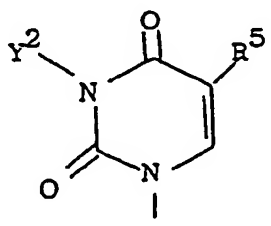
m represents 0 or 1;

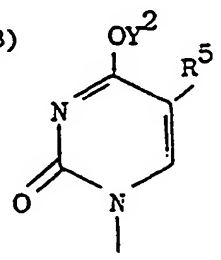
R^1 represents an optionally unsaturated and/or optionally substituted alkyl, alkyloxyalkyl or aryl group or an N-(C_1-C_7 alkyl)-1,4-dihydropyridin-3-yl group or, when n represents 0, H;

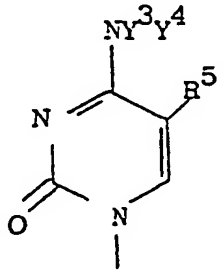
R^2 and R^3 independently represents H, C_1-C_6 alkyl C_2-C_6 alkenyl or alkynyl or aryl;

alternatively, two of such substituents may be replaced by an alkylidene group; and

X represents a group selected from:

(A) 

(B) 

(C) 

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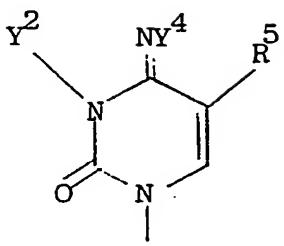

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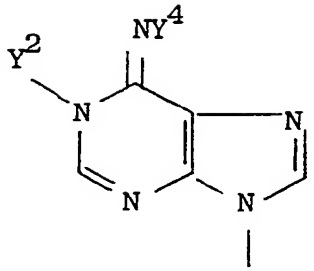

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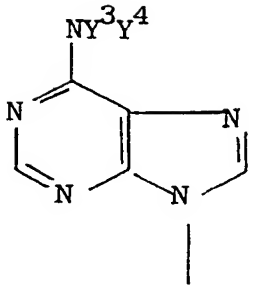

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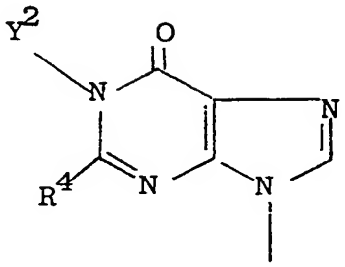

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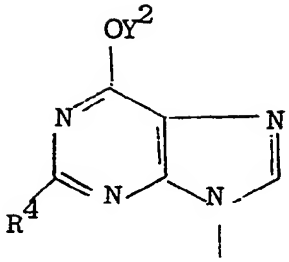

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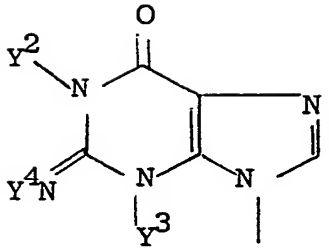
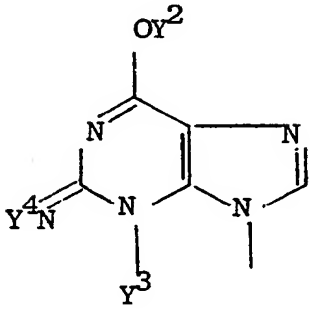


(I)



(J)

wherein

Y^2, Y^3 and Y^4 independently have the same definition as Y^1; R^4 represents H or $-NY^3Y^4$, Y^3 and Y^4 being as defined above; and R^5 represents H or halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl or trifluoromethyl;

provided that at least one of Y^1, Y^2, Y^3 and Y^4 represents other than H and that, when all of Y^2, Y^3 and Y^4 present represent H, then Y^1 represents $R^1(O)_nCO(OCR^2R^3)_m$ wherein n and/or m represents 1; and/or salts thereof.

Preferred stereochemistry in the 1- and 4-position in the cyclopentenyl or cyclopentyl ring is cis, herein designated α. In the cyclopentyl derivatives, the preferred fluorine substitution in the 2-position preferably has the α-configuration and a hydroxyl in the 3-position has the ß-configuration. The ring system thus corresponding to a 2'-deoxy-2-fluoroarabinoside. A fluorine substitution in the 3-position preferably has the ß-configuration corresponding to a 3'-deoxy-3-fluoro-riboside.

It will be appreciated that some of the groups X, for example those in which Y^2 represents a hydrogen atom, are tautomers of other of the groups X and exist in equilibrium therewith.

R^1 preferably represents an optionally unsaturated and/or optionally substituted alkyl or alkyloxyalkyl group containing from 1 to 20 carbon atoms which may be straight or branched, or an aryl group containing from 6 to 20 carbon atoms which may be mono- or poly-cyclic. Substituents which may be present on the alkyl groups R^1 include aryl groups preferably having from 6 to 10 carbon atoms (as in aralkyl groupings), hydroxy and carboxy groups. Aryl groups include 5- or 6-membered heterocyclic aryl groups having one or more heteroatoms selected from O, N and S, such as furyl, imidazolyl, pyrrolyl, pyridinyl and thienyl groups. Substituents which may be present on such aryl groups include alkyl groups, e.g. having from 1 to 6 carbon atoms, hydroxy and carboxy groups. Examples of such groups include methyl, ethyl, propyl, t-butyl, pentyl, stearyl, palmityl, carboxyethyl and benzyl groups.

The alkyl groups R^2, R^3 and R^5 contain from 1 to 6 carbon atoms. However, R^2 preferably represents a hydrogen atom. R^3 preferably represents a hydrogen atom or more preferably a methyl or a ph nyl group. When R^5 represents a halogen atom, it may be fluorine, chlorine, bromine or iodine. However, R^5 preferably represents a hydrogen or chlorine atom or a methyl group. When R^1 in any of the groups Y^1, Y^2, Y^3 or Y^4 represents an N-alkyl-1,4-dihydropyridin-3-yl group, the alkyl group is preferably

methyl.

It will be noted that the present compounds may carry more than one of the groups Y^1, Y^2, Y^3 and Y^4. In such compounds D, E, I and J, it is preferred that m in the group Y^4 represents 0. Groups Y^2 are preferably

$R^1.CO-$, $R^1CO.O.CR^2R^3-$ or $R^1.O.CO.O.CR^2R^3-$.

The salts of the compounds (I) may be acid addition salts with organic or inorganic acids, for instance hydrochloric or phosphoric acid or methanesulphonic acid, ethanedisulphonic acid, 2-naphthalene sulphonic acid, pivalic acid and palmoic acid. Antiviral counter-ions, such as phosphonoformate or suramin, may also be used. Organic or inorganic base salts may be formed with acidic groups present in the molecule; suitable counter-ions include alkali metal ions, such as sodium and potassium ions, divalent ions, such as calcium and zinc ions, and organic ions, such as tetraalkylammonium and choline or ions derived from meglumine or ethylene diamine. Such salts may be formed by reaction of the compound (I) with an appropriate acid or base.

The present invention also relates to the use of above compounds (I) and/or salts therof in the manufacture of a composition for the treatment or prophylaxis of virus infections, in particular neurotropic retro viruses and especially HIV infections. The present invention further relates to such compositions. They may be formulated in conventional manner by admixture of one or more compounds (I) and/or salts thereof with one or more excipients and/or carriers.

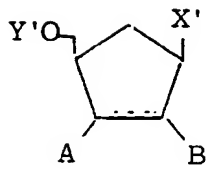
The present compounds (I) may not themselves be inhibitors of reverse transcriptase and may be converted <u>in vivo</u> to the parent nucleoside, for example. Cleavage of the acyl substituents in the heterocycle is by esterases or amidases. The rate of cleavage will depend on the nature of the substituents or whether the acyl group is present on an ester, amide or urethane. The heterocyclic substituted nucleosides with a free 5'-OH group may

be substrates for the kinases as such or may be phosphorylated after initial acyl cleavage. Nevertheless, the substitution at the respective O- and N- atoms gives surprising advantages in terms of uptake and sustained activity. The compounds (I) are more lipophilic than compounds with the free hydroxyl and/or amino functions and this permits rapid and efficient absorption from the gastro-intestinal tract; the absorption rate may be optimised by careful choice of the substituent group to give the desired balance of lipophilicity and hydrophilicity. The lipophilic nature of the compounds (I) also gives the molecules the ability to penetrate the cell membranes more easily and leads to higher intra-cellular concentrations, giving an improved dose/effect ratio. The steady hydrolysis of the compounds ensures a sustained concentration of the active compound in the cell and thereby permits longer intervals between doses, overcoming a significant drawback of the prior art compounds.

Furthermore, the present compounds may penetrate the blood-brain barrier and thus permit treatment of the neurological disorders which have been observed to be related to the presence of neurotropic viruses, e.g. retroviruses, such as HIV, and lentiviruses (Yarchoan et al, The Lancet, January 17, 1987, page 132). This is a significant advantage compared to the compounds with free OH or NH_2 or other antiviral compounds and is not referred to anywhere in the prior art. Attempts have been made to treat these neurological disorders with AZT, but with limited success.

The present invention further relates to a method of treatment of neurological disorders caused by neurotropic viruses wherein an effective dose of a compound (I) or a salt thereof is administered to a patient suffering from such a disorder.

According to the present invention compounds (I) may be prepared in any convenient way, for example, by reaction of a compound corresponding to the following general formula (II):



wherein
Y^1, A and B are as defined above;
and
X^1 is as defined above for X, except that any of Y^1, Y^2, Y^3 and Y^4 may each additionally represent a protecting group;
provided that at least one of Y^1, Y^2, Y^3 and Y^4 represents H;
with a reagent serving to introduce a group $R^1(O)_nCO.(OCR^2R^3)_m$ as defined above, followed, where required, by removal of any protecting group(s) and/or unwanted substituent(s) so introduced.

It should be noted that, when more than one of Y^1, Y^2, Y^3 and Y^4 in the starting material represents hydrogen, multiple reactions may occur.

Where it is desired to ensure that acylation or alkylation is effected while one or more groups Y^1, Y^2, Y^3 and Y^4 remain as hydrogen atoms, it may be desirable to protect the latter first, to form a compound (I) wherein one or more of Y^1, Y^2, Y^3 and Y^4 are protecting groups, these being removed after introduction of the desired acyl or ether group. Such protecting groups may, in fact, be conventional N- or O-protecting groups including groups R^1OCO- which may be selectively removed in the presence of the group(s) intended to remain. Thus, for example, an N-benzyloxycarbonyl may be used to protect an exocylic, amino group and, if the group which is intended to remain is not one which is removable by reduction, for example a straight chain alkoxycarbonyl group, the N-benzyloxycarbonyl group in cyclopentyl may readily be removed selectively using hydrogen and a noble metal catalyst, such as palladium. Silyl protecting groups may also be used, especially for the 5'-oxygen atom, and include trialkylsilyl e.g. trimethylsilyl, dimethyl-t-butylsilyl

and th xyldimethylsilyl groups; for simultaneous protection of the 3'- and 5'- oxygen atoms, the 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane is especially useful.

In general, where more than one of Y^1, Y^2, Y^3 and Y^4 hydrogen, and a mixture of compounds is produced, the individual components may readily be separated, for example by chromatography.

Where 5'-O-monoalkylation is to be effected (i.e. introduction of a group Y^1 wherein m represents 1), it is especially effective to form a dianion of the nucleoside (e.g. by reacting with sodium hydride) and to react this with one equivalent of the alkylating agent. However, in the presence of a second OH group in the cyclopentyl, prior protection of either OH group must be carried out. It is, of course, still possible to use protected forms of the nucleoside, for example by acylation of a nucleophilic nitrogen atom before salt formation with sodium hydride.
Suitable acylating agents for use in the reaction have the formula Ac-L wherein L represents a leaving group. When the acyl group, Ac-, is derived from a carboxylic acid, i.e. corresponds to the formula R^1-CO-, then suitable acylating agents include the acid halides and acid anhydrides advantageously in the presence of a base; when the acyl group is derived from a carbonic acid, i.e. corresponds to the formula R^1.O.CO-, then acylating agents include the haloformate esters, anhydrides and reactive carbonic acid diesters. In such reagents, the halogen may, for example, be chlorine or bromine. The base for use in the reaction with the acid halide or anhydride may, for example, be a heterocyclic base, such as pyridine or 4-dimethylaminopyridine. The latter increases the speed of the reaction and may be used advantageously with pyridine. The reaction will normally be carried out in the presence of an inert solvent, e.g. a substituted amide, such as dimethylformamide and dimethylacetamide, or a halogenated hydrocarbon, such as dichloromethane.

Suitable acyloxyalkylating agents for the present purposes will in general correspond to the formula $R^1CO.O.CR^2R^3L$ or $R^1O-CO-OCR^2R^3L$, wherein L represents a leaving group. Thus, the group L may, for example, be a halogen atom, such as chlorine or bromine or a hydrocarbon-sulphonyloxy group, such as a tosyloxy or mesyloxy group.

The alkylation reaction will normally be effected in the presence of a base, conveniently an inorganic carbonate, such as potassium carbonate, or an alkali metal hydride, such as sodium hydride. Bases as used for acylation may also be useful.

The starting compounds (II) wherein Y^1, Y^2, Y^3 and Y^4 all represent hydrogen atoms are well described in the literature (see for example the literature references cited in the introductory portions). Starting compounds wherein one or more of Y^1, Y^2, Y^3 and Y^4 represent other than hydrogen may be prepared by preliminary reactions as described above.

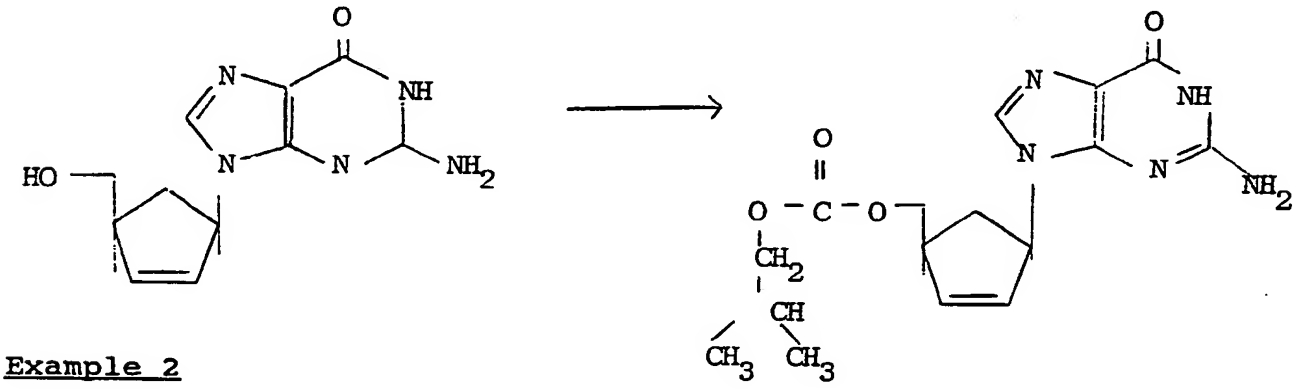
The pharmaceutical compositions according to the present invention may be formulated conventionally by means well known in the art, and may be administered by any convenient route, for instance orally, rectally, vaginally, intraveneously or intramuscularly. Examples of suitable formulations include tablets and capsules, aqueous formulations for intraveneous injection and oil-based formulations for intramuscular injection. Suitable dosages will lie in the range of from 0.1 to 100 mg per kilogram of bodyweight per 24 hour period. The present compositions may also contain other active antivirals for instance acyclovir, phosphonoformate, suramin, Evans Blue, interferons, AZT or the other example mentioned above.

The present invention is further illustrated by the following Examples:

Example 1

(±)-9-[(1α,4α)-4-(isobutyloxycarbonyl)oxymethyl-2-cyclopenten-1-yl]guanine:

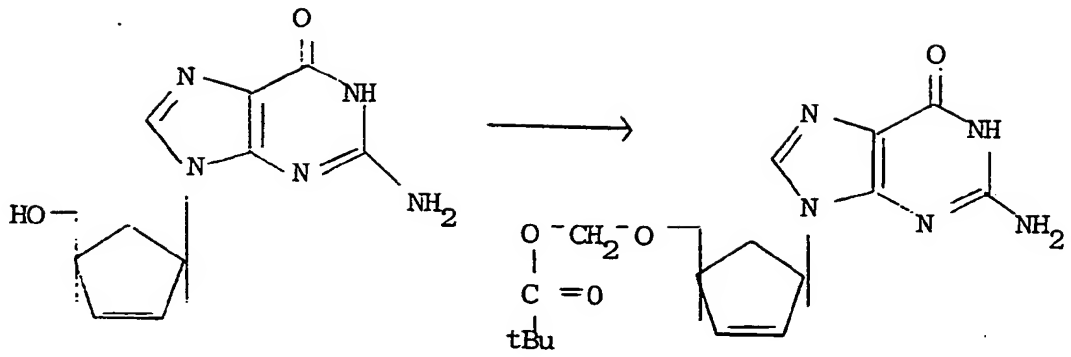
Isobutyl chloroformate (0.7 mmol) is added to an ice-cold mixture of (±)-9-((1α,4α)-4-(hydroxymethyl)-2-cyclopenten-1-yl)guanine (0.5 mmol), N,N-dimethylaminopyridine (0.7 mmol) in acetonitrile (8 ml), the mixture stirred at room temperature for 4 days and the reaction stopped by addition of methanol. The mixture is evaporated to dryness and the product isolated from the residual mixture by chromatography on silica gel using chloroform:methanol (95:5 v/v).



Example 2

(±)-9-[(1α,4α)-4-(pivaloyloxymethyloxymethyl)-2-cyclopenten-1 yl]guanine:

A mixture of (±)-9-[(1α,4α)-4-(hydroxymethyl)-2-cyclopenten-1-yl)]guanine (0.1 mmol), sodium hydride (0.22 mmol; 80 % in oil) in DMF (81.5 ml) is stirred at 0°C for 1 hour, chloromethyl pivalate (0.11 mmol) added and the mixture stirred at 0°C for 5 hours. The reaction is stopped by addition of 1 M aqueous ammonium chloride (6 ml). The mixture is extracted with diethyl ether, the ether extracts washed (saturated NaCl), dried, evaporated and the product fractionated by silica gel chromatography. The d sired product is eluated by chloroform:methanol (98:2 v/v).



Example 3

(±)-9-{(1α,4α)-4-[1-(ethyloxycarbonyloxy)ethyl)oxymethyl]-2-cyclopenten-1-yl}-N^2-isobutyrylguanine:

A mixture of (±)-9-[(1α,4α)-4-(hydroxymethyl)-2-cyclopenten-1-yl]guanine (0.2 mmol) and hexamethyldisilazane (2 ml) in dry DMF (2 ml) is stirred at room temperature for 10 hours, cooled to 10-15°C, pyridine (2 ml) and isobutyric anyhydride (3 ml) added, the mixture stirred at room temperature for 20 hours, cooled to 0-5°C, and treated dropwise with methanol (4 ml). After stirring for 4 hours, the mixture is evaporated under reduced pressure and the residue chromatographed on silica using chloroform:methanol (9:1 v/v) to give (±)-9-[(1α,4α)-4-(hydroxymethyl)-2-cyclopenten-1-yl]-N^2-isobutyrylguanine.

A mixture of (±)-9-[(1α,4α)-4-(hydroxymethyl)-2-cyclopenten-1-yl]-N^2-isobutyrylguanine (0.1 mmol), sodium hydride (0.22 mmol; 80 % in oil) in DMF (81.5 ml) is stirred at 0°C for 1 hour, 1-chloroethyl ethyl carbonate (0.11 mmol) added, the mixture stirred at 0°C for 1 hour and at 20-60°C for 24 hours. The reaction is stopped by addition of 1 M aqueous ammonium chloride (6 ml). The mixture is extracted with diethyl ether, the ether extracts washed (saturated NaCl), dried, evaporated and the product fractionated by silica gel chromatography. The desired product is eluated by chloroform:methanol (98:2 v/v).

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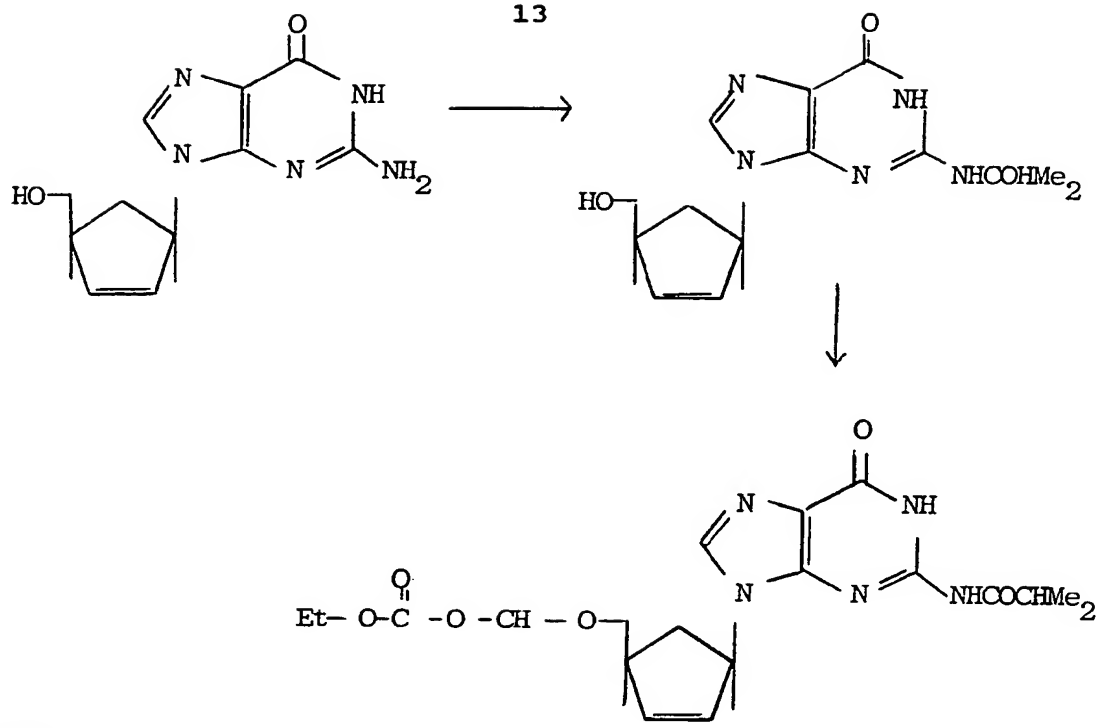


Example 4

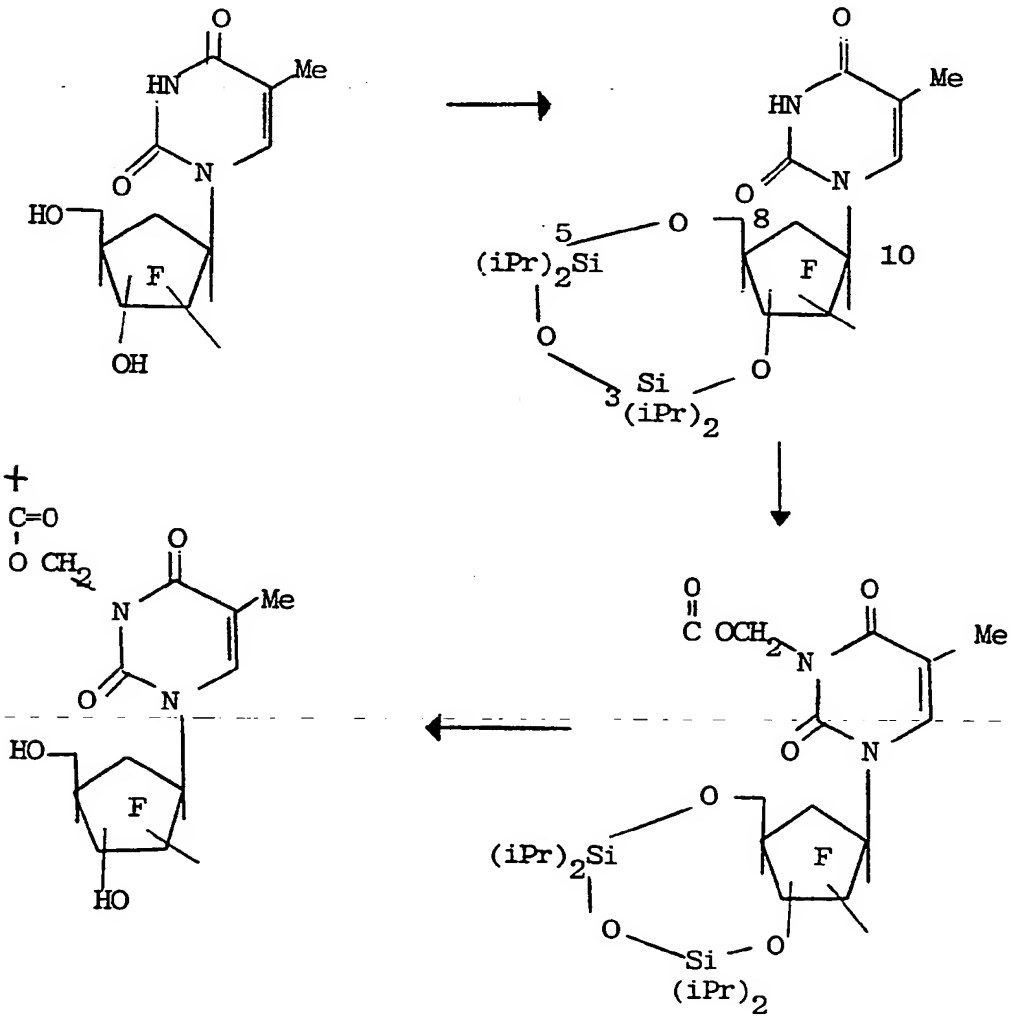
(±)-1-[(1α,2α,3ß,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-5-methyl-3-pivaloyloxymethyluracil:

(±)-1-[(1α,2α,3ß,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl) cyclopentyl]-5-methyluracil (0.2 mmol) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.2 mmol) are added to pyridine (2 ml), the reaction mixture stirred at ambient temperature for 8 hours, the solvent removed under reduced pressure, chloroform (15 ml) added to the residue, washed with aqueous bicarbonate and with water, and the dried ($MgSO_4$) solution evaporated. The residue is chromatographed on silica gel using ethyl acetate-hexane to furnish (±)-1-[(1ß,8α,10α,11α)-11-fluoro-3,3,5,5-tetraisopropyl-2,4,6-trioxa-3,5-disilabicyclo[6,3,0]undecan-10-yl]-5-methyluracil.

The thus-prepared product (0.1 mmol) and potassium carbonate (0.12 mmol) are added to DMF (1 ml), the mixture stirred for 1.5 hours at ambient temperature, cooled to 0°C, chloromethyl pivalate (0.12 mmol) added, the mixture stirred at ambient temperature for 18 hours, the solvent evaporated under reduced

pressure and the residue chromatographed on silica gel using ethyl acetate-hexane to furnish (±)-1-[(1ß,8α,10α,11α)-11-fluoro-3,3,5,5-tetraisopropyl-2,4,6-trioxa-3,5 disilabicyclo [6,3,0]undecan-10-yl]-5-methyl-3-pivaloyloxymethyluracil.

The silyl group is removed by dissolution of the thus-obtained product (1 mmol) in THF (1 ml) and adding 0.25 M solution of tetrabutylammonium fluoride in THF (1 ml). The mixture is stirred at ambient temperature for 30 minutes, the solvent evaporated, the residue dissolved in chloroform (10 ml), washed with water (2 ml), dried ($MgSO_4$), evaporated, and the product purified by chromatorgraphy on silica gel using chloroform:methanol (95:5 v/v).

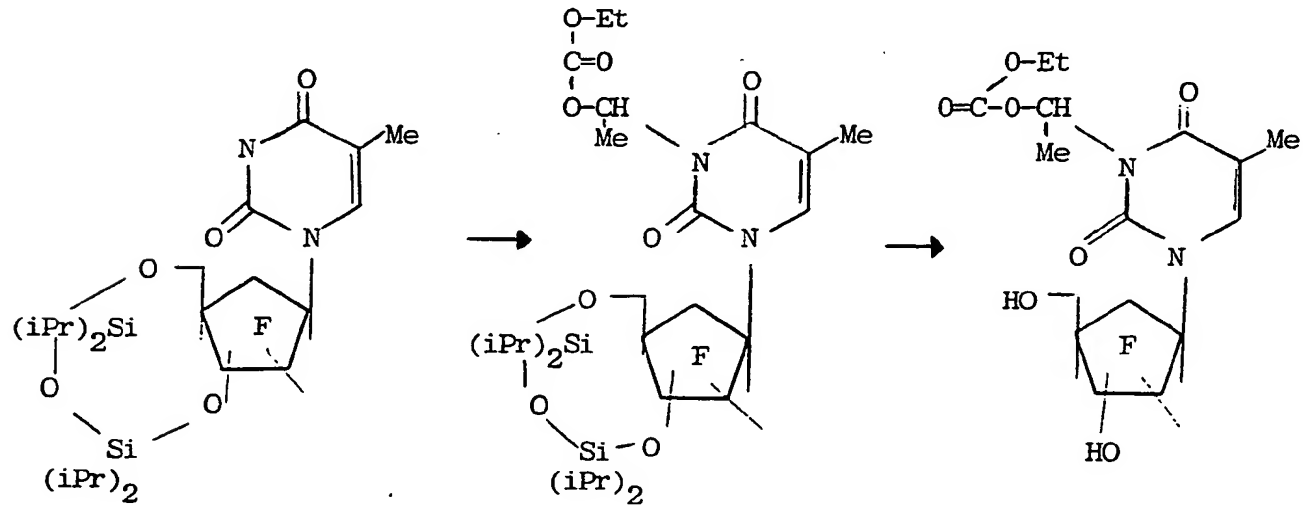


Example 5

(±)-3-[1-(ethyloxycarbonyloxy)ethyl]-1-[(1α,2α,3ß,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-5-methyluracil:

(±)-1-[(1ß,8α,10α,11α)-11-flouro-3,3,5,5-tetraisopropyl-2,4,6-trioxa-3,5-disilabicyclo[6,3,0]undecan-10-yl]-5-methyluracil (0.2 mmol) and potassium carbonate (0.25 mmol) are suspended in DMF (2 ml), the mixture stirred at ambient temperature under nitrogen for 1.5 hours, cooled to 0°C, 1-chloroethyl ethyl carbonate (0.25 mmol) added, the mixture stirred at 0°C for 30 minutes, at ambient temperature for 2 hours, at 60 °C for 24 hours, and the solvent evaporated under reduced pressure. The product (±)-3-[1-(ethyloxycarbonyloxy)ethyl]-1-[(1ß,8α,10α,11α)-11-fluoro-3,3,5,5-tetraisopropyl-2,4,6-trioxa-3,5-disilabicyclo[6,3,0]undecan-10-yl]-5-methyluracil is purified by chromatography on silica gel using ethyl acetate-hexane.

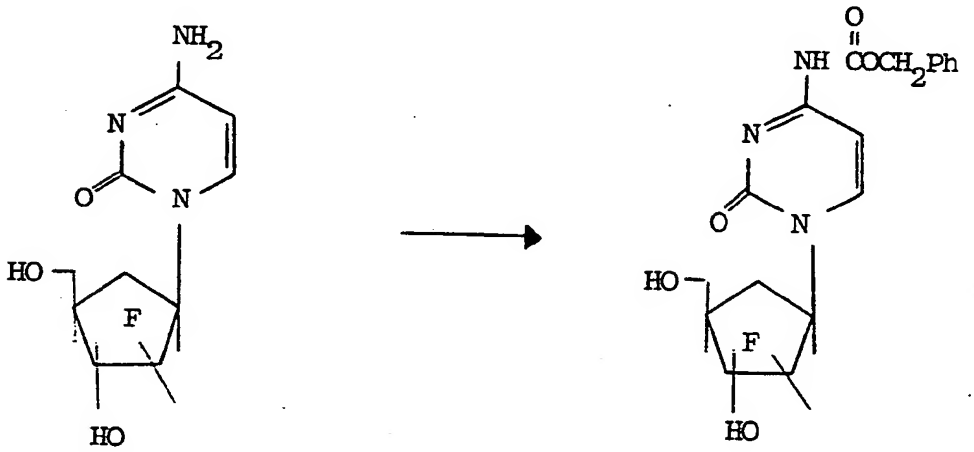
The silyl group is removed by dissolution of the thus-obtained product (1 mmol) in THF (1 ml) and adding 0.25 M solution of tetrabutylammonium fluoride in THF (1 ml). The mixture is stirred at ambient temperature for 30 minutes, the solvent evaporated, the residue dissolved in chloroform (10 ml), washed with water (2 ml), dried ($MgSO_4$), evaporated, and the product purified by chromatography on silica gel using chloroform:methanol (95:5 v/v).



Example 6

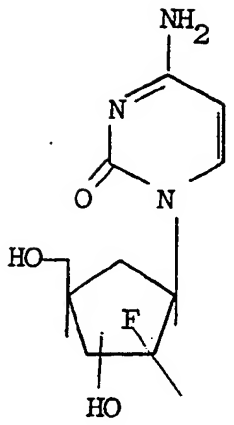
N^4-benzyloxycarbonyl-1-[(1α,2α,3β,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]cytosine.

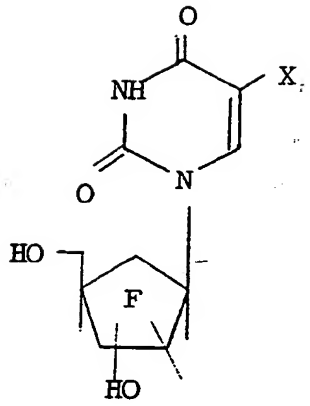
1-[(1α,2α,3β,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]cytosine (0.2 mmol) is dissolved in a mixture of pyridine (0.5 ml) and DMF (0.5 ml), the solution cooled to 0°C, benzyl chloroformate (0.5 mmol) and 4-N,N-dimethylaminopyridine (0.2 mmol) added, the mixture stirred at ambient temperature for 12 hours, water (4 ml) added, the mixture evaporated under reduced pressure, and the residue chromatographed on silica gel. The product is eluted using chloroform:ethanol (99:1 v/v).



The 2-fluoro carbocyclic nucleosides are analogues of 2-fluoroarabinosyl pyrimidine or purine nucleosides:

(±)-4-amino-1-((1α,2α,3β,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl))-2(1H)-pyrimidinone





X represents H:

(±)-1-[(1α,2α,3ß,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1H,3H)-pyrimidinedione

X represents I:

(±)-1-[(1α,2α,3ß,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-2,4(1H,3H)-pyrimidinedione

X represents Me:

(±)-1-[(1α,2α,3ß,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1H,3H)-pyrimidinedione

See Borthwick, A.D., et al, J. Med. Chem., 33, 179, (1990).

(±)-9-[(1α,2α,3ß,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]guanine

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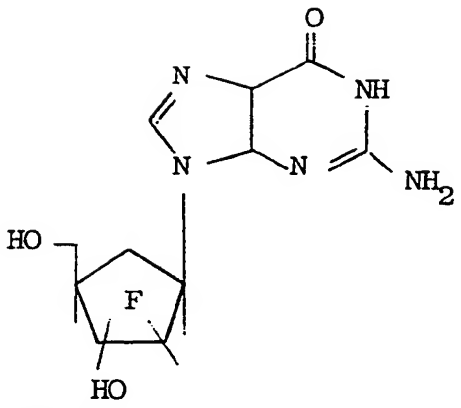
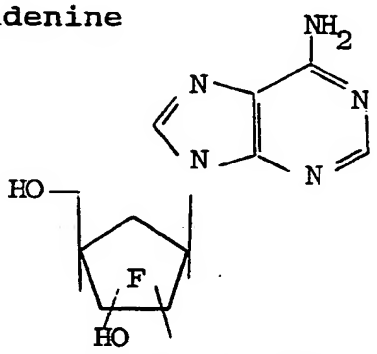


See Borthwick, A.D., et al, J. Chem. Soc., Chem. Comm., 656, (1988).

(±)-9-[(1α,2α,3β,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl) cyclopentyl)]adenine



See Biggadike, K., et al, J. Chem. Soc., Chem. Comm., 898, (1988).

SUBSTITUTE SHEET

(±)-9-[(1α,4α)-4-(ethyloxycarbonyl)oxymethyl-2-cyclopenten-1-yl]guanine:

1-Methylimidazole (100 µl, 1.2 mmol) was added to a solution of ethyl chloroformate (90 µl, 0.94 mmol) in dry DMSO (2 ml). The mixture was stirred at R.T. for 30 min before a solution of (±)-9-[(1α,4α)-4-(hydroxymethyl)-2-cyclopenten-1-yl]guanine (99 mg, 0.40 mmol) in DMSO (1 ml) was added. The mixture was stirred at R.T. overnight before the solvent was removed at reduced pressure. The product was isolated from the residue by reverse phase chromatography on a C-8 column using MeOH:H_2O (3:1), followed by chromatography on silica gel using $CHCl_3$:MeOH (3:1); white solid, yield 55 mg. ^1H NMR (200 MHz, DMSO-d_6): δ 1.2 and 4.10 (OCH_2CH_3), 1.6 and 2.7 (2H, m, H5'), 3.1 (1H, m, H4') 4.15 (2H, m, O-CH_2-CH), 5.4 (1H, m, H1'), 5.9 and 6.1 (2H, m, H2'/3'), 6.4 (2H, s, NH_2), 10.6 (1H, s, NH).

(±)-9-[(1α,4α)-4-(pivaloyloxymethyl)oxymethyl-2-cyclopenten-1-yl]guanine:

A solution of (±)-9-[(1α,4α)-4-(hydroxymethyl)-2-cyclopenten-1-yl]guanine (124 mg, 0.50 mmol) in dry DMSO (0.5 ml) was added dropwise to dimsyl sodium which was generated from sodium hydride (60% in oil: 50 mg, 1.2 mmol) and DMSO (2 ml) with sitrring at R.T. The mixture was stirred at R.T. for 15 min before a solution of chloromethyl pivalate (80 µl, 0.55 mmol) in DMSO (0.5 ml) was added. The mixture was stirred overnight at R.T., saturated ammonium chloride solution added and the reaction mixture evaporated to dryness at reduced pressure. The product was isolated by reverse phase chromatography on a C-8 column using MeOH:H_2O (3:1). The product, 80 mg, was a white solid. ^1H NMR (200 MHz, DMSO-d_6): δ 1.13 (9H, s, piv.), 1.6 and 2.6 (2H, m, H5'), 3.0 (1H, m, H4'), 3.6 (2H, m, O-CH_2-CH), 5.2 (2H, m, O-CH_2-O), 5.9 and 6.1 (2H, m, H2'/3'), 6.5 (2H, s, NH_2), 7.54 (1H, s, H8), 10.6 (1H, br. s, NH).

(±)-9-[(1α,4α)-4-hydroxymethyl-2-cyclopenten-1-yl]-O^6-pivaloyloxymethylguanine:

The title compound was obtained in the above reaction and was the next compound eluated on the C-8 reverse phase column using MeOH:H_2O

(3:1), yield 5 mg. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 (9H, s, piv.), 1.6 and 2.7 (2H, m, H5'), 3.0 (1H, m, H4'), 3.6 (2H, m, C$\underline{H_2}$-CH), 5.2 (2H, m, O-CH_2-O), 5.4 (1H, m, H4'), 5.9 and 6.1 (2H, m, H2'/3'), 7.6 (1H, s, H8).

(±)-9-[(1α,4α)-4-(ethyloxycarbonyl)oxymethyl-2-cyclopenten-1-yl]-N^2-pivaloyl-guanine:

Sodium hydride (60% in oil; 4 mg, 0.1 mmol) was added to a solution of (±)-9-[(1α,4α)-4-(ethyloxycarbonyl)oxymethyl-2-cyclopenten-1-yl]guanine (20 mg, 0.063 mmol) in DMF (1.5 ml). The mixture was stirred at R.T. for 45 min and a solution of chloromethyl pivalate (12 µl, 0.083 mmol) in DMF (1 ml) added. The mixture was stirred at R.T. overnight, the solvent removed at reduced pressure and the residue subjected to reverse phase chromatorgraphy on a C-8 column chromatography using EtOH:$CHCl_3$(1:5). The product was a white solid, yield 5 mg. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 and 4.1 (OCH_2CH_3), 1.3 (9H, s, piv.), 1.7 and 2.8 (2H, m, H5'), 3.1 (1H, m, H4'), 4.2 (2H, m, OC$\underline{H_2}$CH), 5.6 (1H, m, H1'), 6.0 and 6.2 (2H, m, H2'/3'), 7.9 (1H, s, H8), 11.2 (1H, s, NH), 12.2 (1H, s, NH).

(±)-N^2-ethyloxycarbonyl-9-[(1α,4α)-4-ethyloxycarbonyl)oxymethyl-2-cyclopenten-1-yl]-guanine:

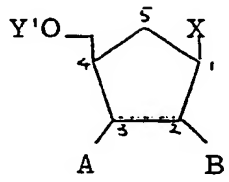
Sodium hydride (60% inoil; 4 mg, 0.1 mmol) was added to a solution of (±)-9-[(1α,4α)-4-(ethyloxycarbonyl)oxymethyl-2-cyclopenten-1-yl]guanine (30 mg, 0.094 mmol) in DMF (1.5 ml), the mixture stirred at room temperature for 45 min, a solution of α-chloroethyl ethyl carbonate (16 µl, 0.12 mmol) in DMF (0.5 ml) added and the mixture stirred at 40°C overnight. The solvent was distilled off at reduced pressure, the product extracted into 15% ethanol in chloroform, the mixture filtered, the filtrate evaporated and the residue subjected to chromatography on silica gel using 15% ethanol in chloroform. Besides the title compound another product due to further alkylation was formed (described below) and was eluated before the title compound. The product was a white solid, yield 8 mg. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 and 1.3 (2 x C$\underline{H_3}$CH$_2$O), 1.7 and 2.7 (2H, m, H5'), 3.2 (1H, m, H4'), 4.1-4.3 (2 x CH_3C$\underline{H_2}$O, C$\underline{H_2}$CH), 5.5 (1H, m, H1'), 6.0 and 6.2(2H, m, H2'/3'), 7.9 (1H,

s, H8), 11.4 (1H, br. s, NH).

(±N^2-ethyloxycarbonyl-O^6-1-(ethyloxycarbonyloxy)ethyl-9-[(1α,4α)-4-(ethyloxycarbonyl)oxymethyl-2-cyclopenten-1-yl]guanine:
The title compound was obtained in the above reaction and was the first product eluated on the silica gel using 15% ethanol in chloroform; yield 2 mg. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 (3 x CH_3CH_2O), 1.7 (3H, d, CH_3CH; 1H, m, H5'), 2.8 (1H, m, H5'), 3.2 (1H, m, H4'), 4.2 (8H, m, CH_2), 5.5 (1H, m, H1'), 7.2 (1H, q, $CHCH_3$), 8.2 (1H, s, H8), 10.3 (1H, s, NH).

Claims:

1. A carbo-nucleoside derivative characterised in that it corresponds to the following general formula:



(I)

wherein

------- represents optional unsaturation;

A represents H or a substituent which is F or OH;

B represents H or a substituent which is F;

Y^1 represents H or a physiologically-acceptable group corresponding to the formula:

$$R^1(O)_nCO(OCR^2R^3)_m-$$

wherein n represents 0 or 1;

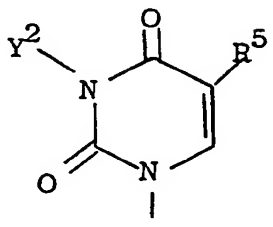
m represents 0 or 1;

R^1 represents an optionally unsaturated and/or optionally substituted alkyl, alkyloxyalkyl or aryl group or an N-(C_1-C_7 alkyl)-1,4-dihydropyridin-3-yl group or, when n represents 0, H;

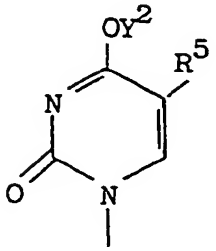
R^2 and R^3 independently represents H, C_1-C_6 alkyl C_2-C_6 alkenyl or alkynyl or aryl;

alternatively, two of such substituents may be replaced by an alkylidene group; and

X represents a group selected from:



(A)



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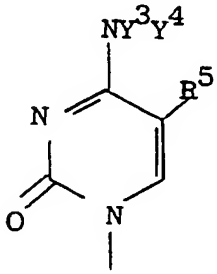
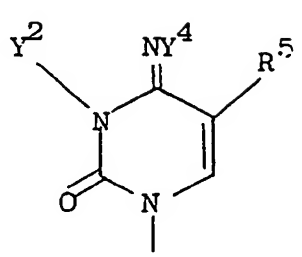
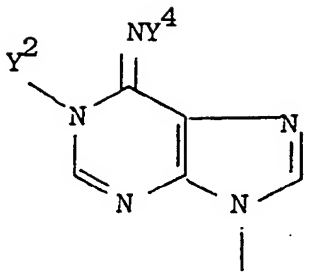


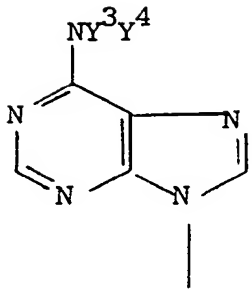
(C)



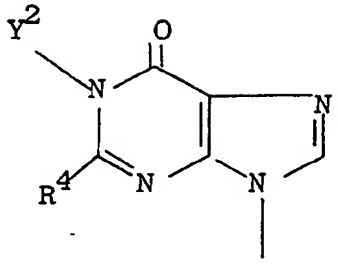
(D)



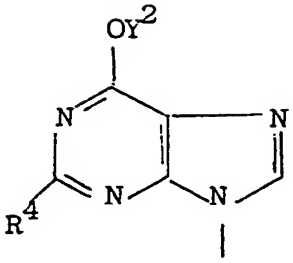
(E)



(F)



(G)



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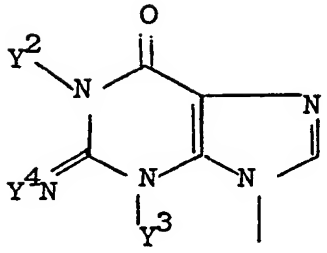
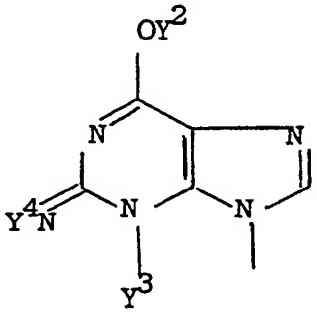


(I)



(J)

wherein

Y^2, Y^3 and Y^4 independently have the same definition as Y^1; R^4 represents H or $-NY^3Y^4$, Y^3 and Y^4 being as defined above; and R^5 represents H or halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl or trifluoromethyl;

provided that at least one of Y^1, Y^2, Y^3 and Y^4 represents other than H and that, when all of Y^2, Y^3 and Y^4 present represent H, then Y^1 represents $R^1(O)_nCO(OCR^2R^3)_m$ wherein n and/or m represents 1; and/or salts thereof.

2. A derivative as claimed in claim 1 wherein for, a saturated compound, if B represents F, A represents OH, or, for an unsaturated compound, A or B represents F and the other represents H.

3. A derivative as claimed in claim 1 or claim 2 wherein there is 2,3-unsaturation.

4. A composition characterised in that it comprises one or more derivatives as claimed in any of claims 1 to 3 and/or salts thereof and one or more excipients and/or carriers.

5. The use of a derivative as claimed in any of claims 1 to 3 and/or a salt thereof or a composition as claimed in claim 4 for the treatment and/or prophylaxis of virus infections.

6. The use of a derivative as claimed in any of claims 1 to 3 and/or a salt thereof for the manufacture of a medicament for the treatment and/or prophylaxis of virus infections.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00655

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 473/00 C 07 D 239/54 C 07 D 239/46
A 61 K 31/52 A 61 K 31/505

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 473/00 C 07 D 239/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	US,A,4719214 (Y. FULMER SHEALY et al.) 12 January 1988, see complete specification	1-6
X	US,A,4396623 (Y. FULMER SHEALY et al.) 2 August 1983, see complete specification	1-6
A	EP,A,0042596 (REGENTS OF THE UNIVERSITY OF MINNESOTA) 30 December 1981, see complete specification	1-6
A	WO,A,8910367 (SCHERING) 2 November 1989, see pages 25-32, claims	1
A	WO,A,8807532 (NYCOMED A.S.) 6 October 1988, see complete specification	1-6

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20-08-1991	23 SEP 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS T TAZELAAR

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9100655 SA 48211

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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